THE CLAIMS

We claim:

1. An amphiphilic drug-oligomer conjugate comprising a therapeutic compound conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled to a hydrophilic moiety.

2. The amphiphilic drug-oligomer conjugate of claim 1 further characterized in that said conjugate exhibits activity without cleavage of the therapeutic compound from the oligomer.

3. The amphiphilic drug-oligomer conjugate of claim 1 further characterized in that said therapeutic compound does not exhibit activity without cleavage of the therapeutic compound from the oligomer.

4. The amphiphilic drug-oligomer conjugate of claim 1 wherein the therapeutic compound is a peptide or protein.

5. The amphiphilic drug-oligomer conjugate of claim 1 wherein the therapeutic compound is a peptide and the peptide is selected from the group consisting of: enkephalin, adrenocorticotropic hormone, adenosine deaminase ribonuclease, alkaline phosphatase, angiotensin, antibodies, arginase, arginine deaminease, asparaginase, caerulein, calcitonin, chemotrypsin, cholecystokinin, clotting factors, dynorphins, endorphins, endorphins, enkephalins, enkephalins, erythropoietin, gastrin-releasing peptide, glucagon, hemoglobin, hypothalmic releasing factors, interferon, katacalcin, motilin, neuropeptide Y, neurotensin, non-naturally occurring opioids, oxytosin, papain, parathyroid hormone, peptides prolactin, soluble CD-4, somatomedin, somatostatin, somatostatin, somatotropin, superoxide dismutase, thyroid stimulating hormone, tissue plasminogen activator, trypsin, vasopressin and analogues and active fragments thereof.

6. The amphiphilic drug-oligomer conjugate of claim 1 wherein the therapeutic compound is an Opioid receptor agonist, antagonist or partial agonist/partial antagonist.

7. The amphiphilic drug-oligomer conjugate of claim 1 wherein the therapeutic compound is [met^5]enkephalin.

8. The amphiphilic drug-oligomer conjugate of claim 1 wherein the lipophilic moiety is coupled to the hydrophilic moiety by a hydrolyzable bond.

9. The amphiphilic drug-oligomer conjugate of claim 1 wherein the lipophilic moiety is coupled to the hydrophilic moiety by a non-hydrolyzable bond.

10. The The amphiphilic drug-oligomer conjugate of claim 1 wherein the lipophilic moiety is coupled to the hydrophilic moiety by a bond selected from the group consisting of: amide bond, carbamate bond, carbonate bond and ester bond.

11. The amphiphilic drug-oligomer conjugate of claim 1 wherein the oligomer moiety is coupled to the drug moiety by a bond selected from the group consisting of amide bond, carbamate bond, carbonate, and ester.

12. The amphiphilic drug-oligomer conjugate of claim 1 wherein the lipophilic moiety is selected from the group consisting of fatty acids, $C_{1\text{-}26}$alkyls, cholesterol, and adamantane.

13. The amphiphilic drug-oligomer conjugate of claim 1 wherein the hydrophilic moiety is selected from the group consisting of sugars or $PEG_{1\text{-}7}$.

14. The amphiphilic drug-oligomer conjugate of claim 1 wherein the hydrophilic moiety comprises a sugar and the sugar is selected from the group consisting of: amino sugars and non-amino sugars.

15. The amphiphilic drug-oligomer conjugate of claim 1 wherein the oligomer is selected from the group consisting of:

$CH_3(CH_2)_n(OC_2H_4)_mOH$ (Formula 1);

wherein n=3 to 25 and m=1 to 6;

$CH_3(CH_2)_n(OC_2H_4)_mOCH_2CO_2H$ (Formula 2);

wherein n=3 to 25 and m=1 to 7;

$CH_3(CH_2)_nCX(OC_2H_4)_mOH$ (Formula 3);

wherein n=3 to 25 , m=1 to 7 and X=O or N;

$R\text{-}(OC_2H_4)_mCH_2CO_2H$ (Formula 4)

wherein m=0 to 5 and R=cholesterol or adamantane; or

$R\text{-}OCO(C_2H_4O)_mCH_2CO_2H$ (Formula 5);

wherein m=0 to 5;

$CH_3(CH_2—CH=CH)_6(CH_2)_2CH_2(OC_2H_4)_mOH$ (Formula 6);

wherein m=0 to 7;

$CH_3(CH_2—CH=CH)_6(CH_2)_2C_X(OC_2H_4)_mOH$ (Formula 7);

wherein m=1 to 7 and X=N or O.

16. The method of claim 1 wherein the hydrophilic moiety comprises a sugar and the sugar is selected from the group consisting of amino sugars and non-amino sugars.

17. The method of claim 1 wherein the hydrophilic moiety comprises a monosaccharide.

18. An amphiphilic drug-oligomer conjugate of claim 1 wherein the oligomer is selected from the group consisting of:

$CH_3(CH_2CH=CH)_6(CH_2)_2CH_2(OC_2H_4)_mOH$,

where m=1 to 7;

$CH_3(CH_2CH=CH)_6(CH_2)_2CO(OC_2H_4)_mOH$,

where m=1 to 7;

$CH_3(CH_2CH=CH)_6(CH_2)_2CONHCH_2CH_2(OC_2H_4)_mOH$,

where m=1 to 6;

$CH_3(CH_2CH=CH)_6(CH_2)_3(OC_2H_4)_mOCH_2COOH$,

where m=1 to 6;

$CH_3(CH_2CH=CH)_6(CH_2)_2CO(OC_2H4)_mOCH_2COOH$,

where m=1 to 6;

$CH_3(CH_2)_7CH=CH(CH_2)_8(OC_2H_4)_mOH$,

where m=1 to 7;

$CH_3(CH_2)_7CH=CH)(CH_2)_7CO(OC_2H_4)_mOH$,

where m=1 to 7;

$CH_3(CH_2)_7CH=CH(CH_2)_7CONHCH_2CH_2(OC_2H_4)_mOH$,

where m=1 to 6;

$CH_3(CH_2)_7CH=CH(CH_2)_8(OC_2H_4)_mOCH_2COOH$,

where m=1 to 6;

$CH_3(CH_2)_7CH=CH(CH_2)_7CO(OC_2H_4)_mOCH_2CH_2OH$,

where m=1 to 6;

$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CH_2(OC_2H_4)_mOH$,

where m=1 to 6;

$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO(OC_2H_4)_mOH$,

where m=1 to 7;

$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CONHCH_2CH_2(OC_2H_4)_mOH$,

where m=1 to 6;

$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO(OC_2H_4)_mOCH_2COOH$,

where m=1 to 6;

$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CH_2(OC_2H_4)_mOCH_2COOH$,

where m=1 to 6;

$CH_3(CH_2CH=CH)_3(CH_2)_7CH_2(OC_2H_4)_mOH$

where m=1 to 7;

$CH_3(CH_2CH=CH)_3(CH_2)_7CO(OC_2H_4)_mOH$,

where m=1 to 7;

$CH_3(CH_2CH=CH)_3(CH_2)_7CONHCH_2CH_2(OC_2H_4)_mOH$,

where m=1 to 6;

$CH_3(CH_2CH=CH_3(CH_2)_7CO(OC_2H_4)_mOCH_2COOH$,

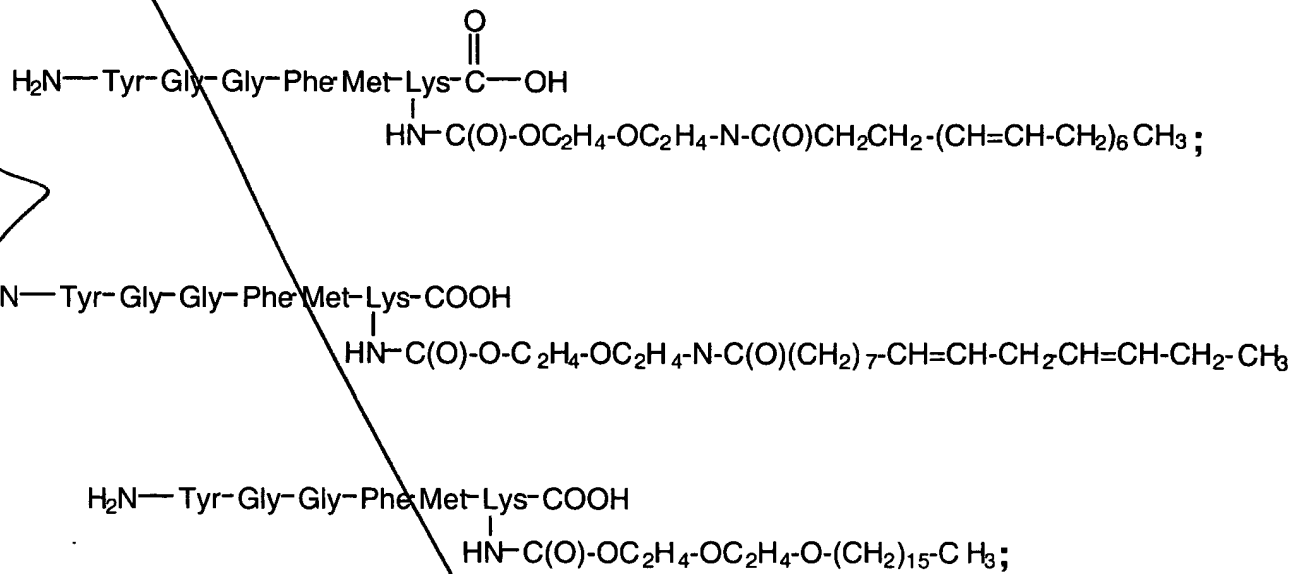
where m=1 to 6; and

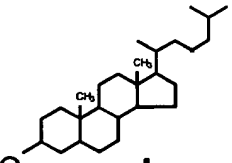
$CH_3(CH_2CH=CH_3(CH_2)_7CH_2(OC_2H_4)_mOCH_2COOH$,

where m=1 to 6.

19. The amphiphilic drug-oligomer conjugate of claim 1 wherein the therapeutic compound is a peptide having an added N-terminal residue selected from the group consisting of proline or alanine.

20. An amphiphilic oligomer-enkephalin conjugate selected from the group consisting of:





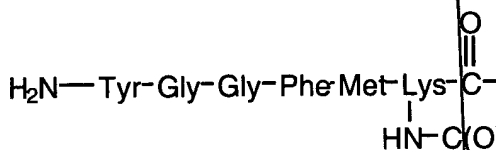
H_2N-Tyr-Gly-Gly-Phe-Met-Lys-COOH
HN-C(O)-O-CH_2-$(C_2H_4O)_2$-CH_2-C(O)-O ;

H_2N-Tyr-Gly-Gly-Phe-Met-Lys-COOH
HN-C(O)-O-$(C_2H_4O)_3$-C(O)-$CH_2)_{14}$-CH_3 ;

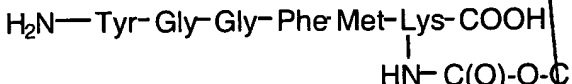
; and

C(O)-O-$(OC_2H_4)_3$-C(O)-$(CH_2)_{14}$-CH_3
HN-Tyr-Gly-Gly-Phe-Met-Lys-COOH
HN-C(O)-O-$(OC_2H_4)_3$-C(O)-$(CH_2)_{14}$-CH_3 .

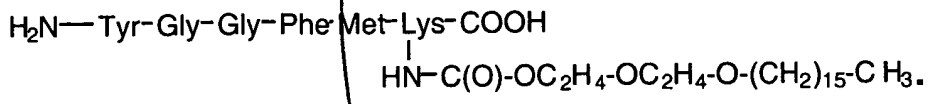
21. An amphiphilic oligomer-enkephalin conjugate wherein the oligomer is comprised of a lipophile and a hydrophile and the lipophile is coupled to the hydrophile by a hydrolyzable bond, said conjugate being selected from the group consisting of:



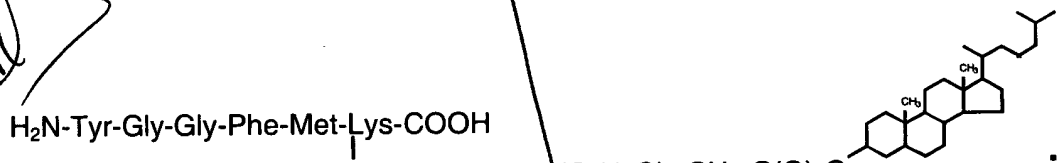
H_2N—Tyr-Gly-Gly-Phe-Met-Lys-C—OH
HN-C(O)-OC_2H_4-OC_2H_4-N-C(O)CH_2CH_2-(CH=CH-$CH_2)_6$ CH_3 ;



H_2N—Tyr-Gly-Gly-Phe-Met-Lys-COOH
HN-C(O)-O-C_2H_4-OC_2H_4-N-C(O)$(CH_2)_7$-CH=CH-CH_2CH=CH-CH_2-C; and



22. An amphiphilic oligomer-enkephalin conjugate wherein the oligomer is comprised of a lipophile and a hydrophile and the lipophile is coupled to the hydrophile by a non-hydrolyzable bond, said conjugate being selected from the group consisting of:



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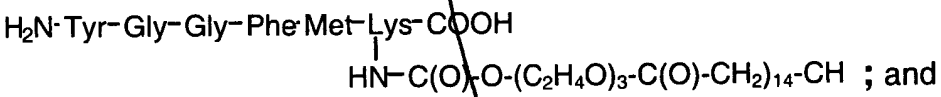
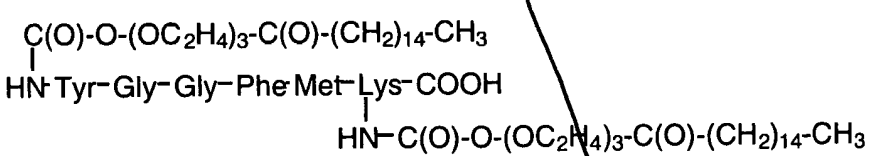


; and



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23. A method for activating a receptor comprising bringing said receptor into contact with an amphiphilic drug-oligomer conjugate comprising a therapeutic compound conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled with to a hydrophilic moiety.

24. The method of claim 18 further characterized in that said conjugate exhibits activity in the without cleavage of the therapeutic compound from the oligomer.

25. The method of claim 18 wherein the receptor is a G-protein coupled receptor.

26. The method of claim 18 wherein the receptor is an Opioid receptor.

27. The method of claim 18 wherein the receptor is a Opioid receptor; selected from the group consisting of δ, μ, and κ.

28. The method of claim 18 wherein the hydrophilic moiety is selected from the group consisting of sugar and PEG_{1-7}.

29. The method of claim 18 wherein the hydrophilic moiety is selected from the group consisting of fatty acid, alkyl 1-26, cholesterol and adamantane.

30. The method of claim 18 wherein the therapeutic compound is a peptide having an added N-terminal residue selected from the group consisting of proline, and alanine.

31. The method of claim 18 wherein the therapeutic compound is a peptide or protein.

32. The method of claim 18 wherein the therapeutic compound is a peptide and the peptide is selected from the group consisting of: enkephalin, adrenocorticotropic hormone, adenosine deaminase ribonuclease, alkaline phosphatase, angiotensin, antibodies, arginase, arginine deaminease, asparaginase, caerulein, calcitonin, chemotrypsin, cholecystokinin, clotting factors, dynorphins, endorphins, endorphins, enkephalins, enkephalins, erythropoietin, gastrin-releasing peptide, glucagon, hemoglobin, hypothalmic releasing factors, interferon, katacalcin, motilin, neuropeptide Y, neurotensin, non-naturally occurring opioids, oxytosin, papain, parathyroid hormone, peptides prolactin, soluble CD-4, somatomedin, somatostatin, somatostatin, somatotropin, superoxide dismutase, thyroid stimulating hormone, tissue plasminogen

activator, trypsin, vasopressin, and analogues and active fragments of such peptides.

33. The method of claim 18 wherein the amphiphilic oligomer is selected from the group consisting of:

$CH_3(CH_2)_n(OC_2H_4)_mOH$ (Formula 1);

wherein n=3 to 25 and m=1 to 6;

$CH_3(CH_2)_n(OC_2H_4)_mOCH_2CO_2H$ (Formula 2);

wherein n=3 to 25 and m=1 to 7;

$CH_3(CH_2)_nCX(OC_2H_4)_mOH$ (Formula 3);

wherein n=3 to 25 , m=1 to 7 and X=O or N;

$R\text{-}(OC_2H_4)_mCH_2CO_2H$ (Formula 4)

wherein m=0 to 5 and R=cholesterol or adamantane; or

$R\text{-}OCO(C_2H_4O)_mCH_2CO_2H$ (Formula 5);

wherein m=0 to 5;

$CH_3(CH_2—CH=CH)_6(CH_2)_2CH_2(OC_2H_4)_mOH$ (Formula 6);

wherein m=0 to 7;

$CH_3(CH_2—CH=CH)_6(CH_2)_2C_X(OC_2H_4)_mOH$ (Formula 7);

wherein m=1 to 7 and X=N or O.

34. The method of claim 18 wherein the hydrophilic moiety is coupled to the hydrophobic moiety by a hydrolyzable bond.

35. The method of claim 18 wherein the hydrophilic moiety is coupled to the hydrophobic moiety by a non-hydrolyzable bond

36. A method for delivering a therapeutic compound across the blood-brain barrier comprising administering to a subject an amphiphilic drug-oligomer conjugate comprising a therapeutic compound conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled to a hydrophilic moiety.

37. The method of claim 31 wherein the therapeutic compound is a peptide or protein.

38. The method of claim 31 wherein the therapeutic compound is a peptide and the peptide is selected from the group consisting of: enkephalin, adrenocorticotropic hormone, adenosine deaminase ribonuclease, alkaline phosphatase, angiotensin, antibodies, arginase, arginine deaminease, asparaginase, caerulein, calcitonin, chemotrypsin, cholecystokinin, clotting factors, dynorphins, endorphins, endorphins, enkephalins, enkephalins, erythropoietin, gastrin-releasing peptide, glucagon, hemoglobin, hypothalmic releasing factors, interferon, katacalcin, motilin, neuropeptide Y, neurotensin, non-naturally occurring opioids, oxytosin, papain, parathyroid hormone, peptides prolactin, soluble CD-4, somatomedin, somatostatin, somatostatin, somatotropin, superoxide dismutase, thyroid stimulating hormone, tissue plasminogen activator, trypsin, vasopressin, and analogues and active fragments of such peptides.

39. The method of claim 31 wherein the therapeutic compound is [met^5]enkephalin.

40. The method of claim 31 wherein the lipophilic moiety is coupled to the hydrophilic moiety by a hydrolyzable bond.

41. The method of claim 31 wherein the lipophilic moiety is coupled to the hydrophilic moiety by a non-hydrolyzable bond.

42. The method of claim 31 wherein the lipophilic moiety is coupled to the hydrophilic moiety by a bond selected from the group consisting of: amide bond, carbamate bond, carbonate bond and ester bond.

43. The method of claim 31 wherein the oligomer moiety is coupled to the drug moiety by a bond selected from the group consisting of amide bond, carbonate bond, carbamate bond, and ester bond.

44. The method of claim 31 wherein the lipophilic moiety is selected from the group consisting of fatty acids, C_{1-26}alkyls, and colesterol.

45. The method of claim 31 wherein the hydrophilic moiety is selected from the group cobsisting of sugars, and PEG_{1-7}.

46. A method for inducing analgesia in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an amphiphilic drug-oligomer conjugate comprising enkephalin conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled to a hydrophilic moiety.

47. The method of claim 41 wherein the therapeutic compound is [met^5]enkephalin.

48. The method of claim 41 wherein the lipophilic moiety is selected from the group consisting of fatty acids, C_{1-26} alkyls, and cholesterol.

49. The method of claim 41 wherein the one or more hydrophilic moieties are selected from the group consisting of sugars and PEG.

50. The method of claim 41 wherein the hydrophilic moiety comprises a sugar and the sugar is selected from the group consisting of amino sugars and non-amino sugars.

51. The method of claim 41 wherein the oligomer is selected from the group consisting of:

$CH_3(CH_2)_n(OC_2H_4)_mOH$ (Formula 1);

wherein n=3 to 25 and m=1 to 6;

$CH_3(CH_2)_n(OC_2H_4)_mOCH_2CO_2H$ (Formula 2);

wherein n=3 to 25 and m=1 to 7;

$CH_3(CH_2)_nCX(OC_2H_4)_mOH$ (Formula 3);

wherein n=3 to 25 , m=1 to 7 and X=O or N;

$R\text{-}(OC_2H_4)_mCH_2CO_2H$ (Formula 4)

wherein m=0 to 5 and R=cholesterol or adamantane; or

$R\text{-}OCO(C_2H_4O)_mCH_2CO_2H$ (Formula 5);

wherein m=0 to 4 and R=cholesterol or adamantane;

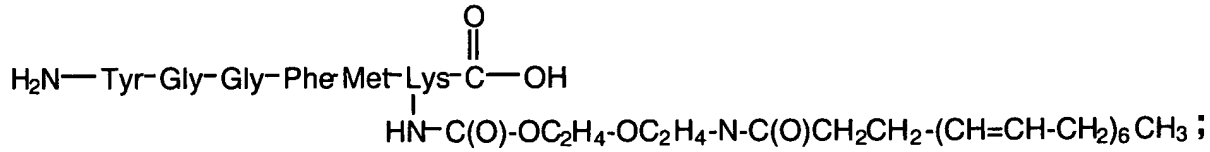
$CH_3(CH_2—CH=CH)_6(CH_2)_2CH_2(OC_2H_4)_mOH$ (Formula 6);

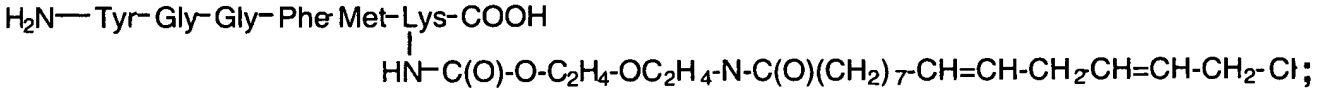
wherein m=0 to 7;

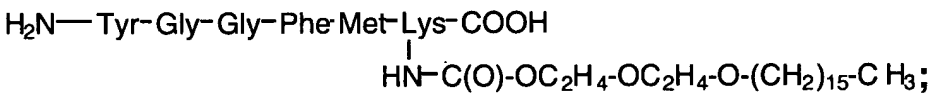
$CH_3(CH_2—CH=CH)_6(CH_2)_2C_X(OC_2H_4)_mOH$ (Formula 7);

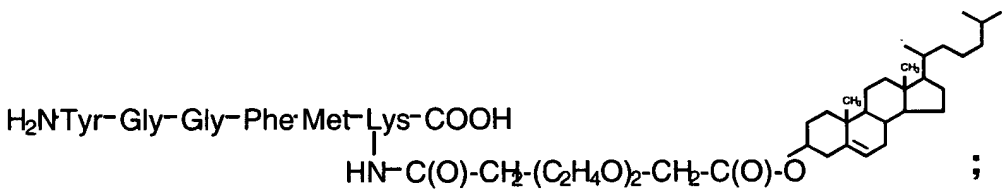
wherein m=1 to 7 and X=N or O.

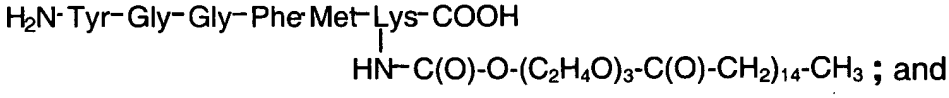
52. An amphiphilic oligomer-enkephalin conjugate selected from the group consisting of:

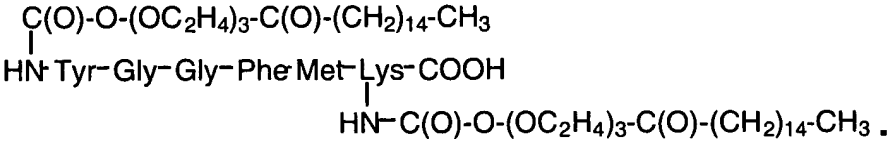












53. A method for altering the binding affinity of a peptide to its receptor comprising conjugating the peptide to an amphiphilic oligomer comprising a lipophilic moiety coupled to a hydrophilic moiety.

54. The method according to claim 48 further characterized in that the binding affinity is increased.

55. The method according to claim 48 further characterized in that the binding affinity is reduced.

56. The method of claim 48 wherein the peptide is a peptide or protein.

57. The method of claim 48 wherein the peptide is selected from the group consisting of: enkephalin, adrenocorticotropic hormone, adenosine deaminase ribonuclease, alkaline phosphatase, angiotensin, antibodies, arginase, arginine deaminease, asparaginase, caerulein, calcitonin, chemotrypsin, cholecystokinin, clotting factors, dynorphins, endorphins, endorphins, enkephalins, enkephalins, erythropoietin, gastrin-releasing peptide, glucagon, hemoglobin, hypothalmic releasing factors, interferon, katacalcin, motilin, neuropeptide Y, neurotensin, non-naturally occurring opioids, oxytosin, papain, parathyroid hormone, peptides prolactin, soluble CD-4, somatomedin, somatostatin, somatostatin, somatotropin, superoxide dismutase, thyroid stimulating hormone, tissue plasminogen activator, trypsin, vasopressin, and analogues and fragments of such peptides.

58. The method of claim 48 wherein the peptides is [met^5]enkephalin.

59. The method of claim 48 wherein the lipophilic moiety is selected from the group consisting of fatty acids, C_{1-26}alkyls, and colesterol.

60. The method of claim 48 wherein the hydrophilic moiety is selected from the group consisting of sugars or PEG_{1-7}.

61. The method of claim 48 wherein the oligomer is selected from the group consisting of:

$CH_3(CH_2)_n(OC_2H_4)_mOH$ (Formula 1),

wherein n=3 to 25 and m=1 to 6;

$CH_3(CH_2)_n(OC_2H_4)_mOCH_2CO_2H$ (Formula 2),

wherein n=3 to 25 and m=1 to 7;

$CH_3(CH_2)_nCX(OC_2H_4)_mOH$ (Formula 3),

wherein n=3 to 25 , m=1 to 7 and X=O or N;

$R\text{-}(OC_2H_4)_mCH_2CO_2H$ (Formula 4),

wherein m=0 to 5 and R=cholesterol or adamantane; or

$R\text{-}OCO(C_2H_4O)_mCH_2CO_2H$ (Formula 5),

wherein m=0 to 5;

$CH_3(CH_2—CH=CH)_6(CH_2)_2CH_2(OC_2H_4)_mOH$ (Formula 6),

wherein m=0 to 7;

$CH_3(CH_2—CH=CH)_6(CH_2)_2C_X(OC_2H_4)_mOH$ (Formula 7),

wherein m=1 to 7 and X=N or O.

62. The amphiphilic drug-oligomer conjugate of claim 1 wherein the therapeutic compound is a peptide and the peptide is selected from the group consisting of:

Ac-Phe-Arg-Trp-Trp-Tyr-Lys—NH_2 ;

Ac-Arg-Trp-Ile-Gly-Trp- Lys —NH_2 ;

Trp-Trp-Pro-Lys-His-Xaa—NH_2 ,

wherein Xaa is a naturally-occurring amino acid;

Trp-Trp-Pro-Xaa—NH_2 ,

wherein Xaa is Lys or Arg;

Tyr-Pro-Phe-Gly-Phe-Xaa—NH_2 ,

wherein Xaa is a naturally-occurring amino acid;

(D)Ile-(D)Met-(D)Ser-(D)Trp-(D)Trp-Gly_n-Xaa—NH_2 ,

wherein n is 0 or 1 and wherein Xaa is Gly or the D-form-of a naturally-occurring amino acid;

(D)Ile-(D)Met-(D)Thr-(D)Trp-Gly-Xaa—NH_2 ,

wherein Xaa is Gly or the D-form of a naturally-occurring amino acid;

Tyr-A1-B2-C3—NH_2 ,

wherein A1 is (D)Nve or (D)Nle,

B2 is Gly, Phe, or Trp, and

C3 is Trp or Nap;

Pm and red {Me_xH_y-Tyr-$(NMe)_z$-Tyr-Xaa_z—NH_2},

x is 0, 1, or 2,

y is 0, 1, or 2, and

z is 0 or 1, and

wherein Xaa is Phe, (D)Phe, or NHBzl, with the proviso that x and y together is never greater than 2;

Trp-Trp-Pro-D4-His_z-Xaa_z—NH_2;

wherein z is 0 or 1,

wherein D4 is Lys or Arg, and

wherein Xaa is a naturally-occurring amino acid.

63. The method of claim 18 wherein the therapeutic compound is a peptide and the peptide is selected from the group consisting of:

Ac-Phe-Arg-Trp-Trp-Tyr-Lys—NH_2;

Ac-Arg-Trp-Ile-Gly-Trp- Lys —NH_2

Trp-Trp-Pro-Lys-His-Xaa—NH_2

wherein Xaa is a naturally-occurring amino acid;

Trp-Trp-Pro-Xaa—NH_2

wherein Xaa is Lys or Arg;

Tyr-Pro-Phe-Gly-Phe-Xaa—NH_2

wherein Xaa is a naturally-occurring amino acid;

(D)Ile-(D)Met-(D)Ser-(D)Trp-(D)Trp-Gly_n-Xaa—NH_2

wherein n is 0 or 1 and wherein Xaa is Gly or the D-form-of a naturally-occurring amino acid;

(D)Ile-(D)Met-(D)Thr-(D)Trp-Gly-Xaa—NH_2

wherein Xaa is Gly or the D-form of a naturally-occurring amino acid;

Tyr-A1-B2-C3—NH_2

wherein A1 is (D)Nve or (D)Nle,

B2 is Gly, Phe, or Trp, and

C3 is Trp or Nap;

Pm and red {Me_xH_y-Tyr-$(NMe)_z$-Tyr-Xaa_z—NH_2},

x is 0, 1, or 2,

y is 0, 1, or 2, and

z is 0 or 1, and

wherein Xaa is Phe, (D)Phe, or NHBzl, with the proviso that x and y together is never greater than 2;

$Trp\text{-}Trp\text{-}Pro\text{-}D4\text{-}His_z\text{-}Xaa_z\text{—}NH_2$,

wherein z is 0 or 1,

wherein D4 is Lys or Arg, and

wherein Xaa is a naturally-occurring amino acid.